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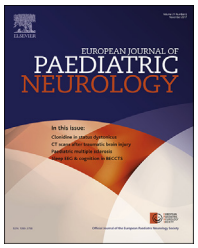

Original article

Usefulness of cocaine drops in investigating infant anisocoria

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ABSTRACT

Introduction: Whereas apraclonidine has eclipsed cocaine test in the exploration of unilateral miosis in adults, its use in infants is avoided because of the risk of central nervous system depression. This chart review evaluates the usefulness of cocaine drops in infants.
Methods: Infants under the age of one referred for unilateral miosis between November 1, 2009 and November 1, 2015, were reviewed. Patients underwent the following protocol: (1) in case of isolated miosis, cocaine test was performed. If the miotic pupil did not dilate, imaging was performed. Dilation in both eyes led to simple clinical follow-up. (2) In case of miosis associated with ptosis or iris heterochromia, imaging of the brain, neck and chest was directly performed.
Results: Twenty-six children were included. Twenty-two presented an isolated miosis; three had ipsilateral ptosis, and one had no pupillary light reflex in the miotic eye. Cocaine tests performed in the 22 patients led to imaging in four, which was always normal. No side effect of the test was noticed. Imaging found one neuroblastoma and one intraorbital hemolymphangioma in two patients presenting miosis plus another sign. Imaging was avoided for 18 patients thanks to negative cocaine test.
Discussion: Urgent imaging is mandatory in infants presenting with miosis associated with other localizing sign on the sympathetic nerve pathway (Horner syndrome). Since the

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uselessness of complementary investigations in isolated infantile miosis cannot be proven so far, cocaine test remains the gold standard, as it is safe, cheaper and less stressful than systematic imaging.

1. Introduction

While the debated question of the management of congenital Horner syndrome has not been solved yet, another situation, far more frequent, is also a matter of controversy for pediatric neurologists and ophthalmologists: infants presenting with an isolated unilateral miosis – by far the most frequent form of infant anisocoria. In these cases, differentiating between a sympathetic dysfunction and a physiological anisocoria is the question that leads – or not – to investigations. In adults, the diagnosis steps in the case of a recently-noticed isolated unilateral miosis are now well established[1]: first, by looking at old pictures on the patient's identity cards, one can often exclude the need of urgent imaging if the anisocoria has actually been present for years. Then, apraclonidine testing is now widely used in the everyday practice. Apraclonidine hydrochloride is an alpha-adrenergic receptor agonist with strong alpha-2 and weak alpha-1 activity, which is used for the treatment of increased intraocular pressure. In a normal pupil, the alpha-1 activity of apraclonidine at a concentration of 0.5% is not strong enough to cause dilation. In Horner syndrome, the sympathetic denervation is responsible for an increased sensitivity of alpha-1 receptors to alpha-1 agonists in the ipsilateral pupil. This local and specific hypersensitivity to alpha-1 agonists leads to a pupil dilation and ptosis resolution that are checked 45 min after instillation of apraclonidine 0.5%. With an overall sensitivity of 87%,[2] this pharmacological test can confirm a diagnosis of Horner syndrome and helpful in the decision of further investigations. In infants, however, the use of alpha agonists is not recommended because of the risk of central nervous system depression. Adverse effects have been reported[3,4] and many specialists therefore avoid taking such risks in infants for a diagnostic procedure. Cocaine drops have been known for years to be the gold standard of pharmacological tests for the diagnosis of Horner syndrome.[5] Cocaine acts by inhibiting the noradrenaline re-uptake into the presynaptic sympathetic neuron, thus revealing the spontaneous activity of the sympathetic pathway to the eye. In case of Horner's syndrome, the absence of sympathetic activity due to denervation will lead to no dilation in the miotic eye, while a normal pupil will dilate, except in some patients from African descent, where cocaine drops may have little or no effect.[6] Measuring the anisocoria 1 h after 2.5–5% cocaine eye drops can therefore distinguish between Horner syndrome and normals: if the anisocoria is equal or superior to 1 mm after cocaine, Horner syndrome can be diagnosed, if anisocoria is less than 0.3 mm, Horner syndrome can be excluded.[6] As cocaine drops are often not easily available for the clinician, the pharmacological tests are often omitted, leading to unnecessary systematic investigations in some cases, or delay in establishing a diagnosis in other cases. Neuroblastoma, one of the most severe causes that can be associated with Horner syndrome in children, can be revealed by an isolated Horner syndrome in 2% of cases.[7] Moreover, two infants presenting with an isolated miosis as the first symptom of a neuroblastoma have been reported.[8] It has been shown that early diagnosis is one of the most important prognostic factor in the management of neuroblastoma, which emphasizes the importance of reliable diagnostic guidelines. However, most infantile anisocoria are believed to be congenital and the vast majority is completely isolated. For these reasons, their current management is in most cases heterogeneous, ranging from simple clinical follow-up to systematic imaging. Urine testing for catecholamines is now recognized as having no indication in this situation, considering its poor sensitivity to detect infant neuroblastomas.[9]

To the best of our knowledge, no study has specifically addressed the question of the management of isolated miosis in children under one year of age. The purpose of this series is to assess the usefulness of cocaine drops, and to evaluate the work-up protocol used in our department in the case of unilateral miosis in infants.

2. Materials and methods

Medical charts of children referred to the neuro-ophthalmology clinic of Necker-Enfants Malades Hospital between November 1, 2009 and November 1, 2015 for unilateral miosis, were retrospectively reviewed. Cases with already known diagnosis explaining anisocoria at first visit, cases referred to our center after having the imaging performed, and cases having presented with miosis after the age of 1, were excluded. All infants underwent the following protocol (Fig. 1): (1) in the case of isolated and significant miosis, cocaine test was performed. The test consisted in three steps: first, observation and photographs of the pupils at baseline in photopic, mesopic and scotopic lighting, then instillation of two cocaine drops in each eye at T0, and finally observation and photographs of the pupils at T0 + 60 min (T60), in the same lighting conditions. Conventional static and dynamic pupillometry was almost never possible both at T0 and T60, because of the age of the infants. Cocaine drops were prepared by the hospital pharmacy (Hôtel-Dieu, AP-HP, Paris) and consisted in a dilution of 5% cocaine in a saline solution. If the drops were immediately available, the test was performed at first visit. If not, the patient was required to come back for a second visit to undergo the test. Drops were instilled by the